

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|--|---|---|
| Applicant's or agent's file reference WST108APCT | FOR FURTHER ACTION | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |
| International application No. PCT/US03/31519 | International filing date (<i>day/month/year</i>) 27 October 2003 (27.10.2003) | (Earliest) Priority Date (<i>day/month/year</i>) 30 October 2002 (30.10.2002) |
| Applicant THE WISTAR INSTITUTE OF ANATOMY AND BIOLOGY | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. Certain claims were found unsearchable (See Box I).

3. Unity of invention is lacking (See Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/31519

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-5, 11-18, 20-24

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

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International application No.

PCT/US03/31519

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01N 33/00; A01K 67/027; C12N 15/00, 15/63, 15/85, 15/87, 15/09, 15/70, 15/74, 5/00, 5/02
 US CL : 800/3, 18, 21, 22, 25; 435/455, 463, 320.1, 325

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 U.S. : 800/3, 18, 21, 22, 25; 435/455, 463, 320.1, 325

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 CAPLUS, MEDLINE, EMBASE, BIOSIS, LIFESCI, WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| Y | RILEY, M.P. et al. Graded Deletion and Virus-Induced Activation of Autoreactive CD4+ T Cells. The J. of Immunology. 2000, Vol 165, pages 4870-4876, see entire | 1-5, 11-18, 20-24 |
| Y | BOT et al. Cellular Mechanisms Involved in Protection Against Influenza Virus Infection in Transgenic Mice Expressing a TCR Receptor Specific for Class II Hemagglutinin Peptide in CD4+ and CD8+ T cells. The J. of Immunology. 1998, Vol 160, pages 4500-4507, see entire document. | 1-5, 11-18, 20-24 |
| Y | SHIH, F.F. et al. A Major T Cell Determinant from the Influenza Virus Hemagglutinin (HA) can be a Cryptic Self Peptide in HA Transgenic Mice. Int. Immunol. February 1997, Vol 9, No. 2, pages 249-261, see entire document. | 1-5, 11-18, 20-24 |
| Y | RILEY, M.P. et al. CD4+ T cells that Evade Deletion by a Self Peptide Display Th1-Biased Differentiation. Eur. J. Immunology. January 2001, Vol. 31, pages 311-319, see entire document. | 1-5, 11-18, 20-24 |

Further documents are listed in the continuation of Box C.

See patent family annex.

| | | | |
|-----|---|-----|--|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" | earlier application or patent published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

Date of the actual completion of the international search

16 March 2004 (16.03.2004)

Date of mailing of the international search report

22 NOV 2004

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group I, claim(s) 1-5, 11-18, drawn to methods for generating a non-human mammalian model of an autoimmune disorder by interbreeding two transgenic mammals of the same species, wherein the first transgenic mammal expresses MHC class I-restricted TCR with high affinity for an A/PR/8 HA peptide S1 and the second transgenic mammal expresses DNA encoding the influenza A/PR/8 HA peptide S1 operably linked to a functional fragment of the MHC class II-I E α promoter, and the model is a high penetrance model of said disorder.

Group II, claim(s) 1, 6-17, 19, drawn to methods for generating a non-human mammalian model of an autoimmune disorder by interbreeding two transgenic mammals of the same species, wherein the first transgenic mammal expresses a MHC class II-restricted TCR with high affinity for a synthetic mutant S1 analog of A/PR/8 HA, but with low affinity for the native A/PR/8HA S1 peptide, and the second transgenic mammal expresses DNA encoding the native influenza A/PR/8 HA peptide S1 operably linked to a functional fragment of the MHC class II-I E α promoter and the model is a low penetrance model of the disorder.

Group III, claim(s) 20-24, drawn to a transgenic non-human mammal that expresses a MHC class II-restricted TCR and expresses a selective peptide that binds to said TCR, wherein the selected peptide is selectively expressed by MHC class II positive APC, wherein said peptide is a naturally occurring, recombinant, or synthetic MHC class II-restricted T cell determinant that specifically binds with high affinity to said TCR, wherein the mammal exhibits high penetrance of said disorder

Group IV, claim(s) 20-23, 25, drawn to transgenic non-human mammal that expresses a MHC class II-restricted TCR and expresses a selective peptide that binds to said TCR, wherein the selected peptide is selectively expressed by MHC class II positive APC, wherein the selected peptide is a naturally occurring, recombinant or synthetic protein or peptide fragment that binds with low affinity to said TCR, wherein the mammal exhibits low penetrance of said disorder..

Group V, claim(s) 26-28, drawn to mammalian cells containing at least one transgene comprising a first nucleic acid sequence that encodes a MHC class II-restricted TCR operably linked to regulatory sequences and a second nucleic acid that encodes a selected peptide that binds to said TCR, operably linked to a sequence that directs expression of said selected peptide selectively to MHC class II positive APCs.

Group VI, claim(s) 29-32, drawn to methods of producing a transgenic non-human mammalian model of an autoimmune disorder.

Group VII, claim(s) 33, drawn to a cell culture derived from tissues of a transgenic non-human mammal.

Group VIII, claim(s) 34-35, drawn to methods of screening a compound for the ability to effect symptoms of an autoimmune disorder.

Group IX, claim(s) 36-38, drawn to a method of identifying a gene product responsible for the development of autoimmune disorders

Group X, claim(s) 39-44, drawn to methods for identifying a biochemical marker of autoimmune disorder.

Group XI, claim(s) 45, drawn to a novel composition for the diagnosis or treatment of inflammatory arthritis.

Unity of Invention between different categories of inventions will only be found to exist if specific combinations of inventions are present. Those combinations include:

- 1) A product and a special process of manufacture of said product
- 2) A product and a process of use of said product
- 3) A product, a special process of manufacture of said product, and a process of use of said product
- 4) A process and an apparatus specially designed to carry out said process
- 5) A product, a special process of manufacture of said product, and an apparatus specially designed to carry out said process.

The allowed combinations do not include multiple products, multiple methods of using said products, and methods of making multiple products as claimed in the instant invention. See MPEP §1850 and 37 CFR 1.475.

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The inventions listed as Groups I-XI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons. Groups I-II, VII, IX-XI are drawn to multiple methods of making and using a non-human mammalian model of an autoimmune disorder, each with specific and materially different protocol that are not required for the implementation of each other. Groups IV-VI, VIII and X are drawn to multiple distinct products that do not share the same inventive concepts that are not required for the implementation of the other.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

NOTESTOFORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.